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EXAMINER	
LIU, SAMUEL W	
ART UNIT	**PAPER NUMBER**
1653	

DATE MAILED: 06/16/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/030,137	STOTT, KELVIN	
	Examiner	Art Unit	
	Samuel W Liu	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 January 2002*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-45* is/are pending in the application.

4a) Of the above claim(s) *29-42,44 and 45* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-28 and 43* is/are rejected.

7)☒ Claim(s) *1-28 and 43* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *5/2/02, 6/11/02 & 5/23/02* .
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the claims

Claims 1-45 are pending.

Applicants' preliminary amendment filed 28 January 2002, which amends claims 3-4, 6-7, 10-11, 13, 15-17, 19, 21-23, 25-27 and 29-44 has been entered. Also, applicants' request for extension of time of one month (filed 13 May 2004) has been entered.

Election/restriction

Applicants' election of Group I, claims 1-28 and 43 with traversal in the response filed 13 May 2004 is acknowledged. The traversal is on the ground(s) that (i) although Quibell teach Nα-substituted polypeptide forming β-structure, the Quibell's molecule (β-amyloid (1-34)) does not allow for association with a target peptide; and thus, the Quibell et al. teach away from the present invention as defined in claim1 (see page 3, the 2nd paragraph); (ii) all of the Nα-substitutes of Quibell reference are removed while the Nα-substitutes of the present invention remains, and, (iii) the Nα-substituted polypeptide taught by Quibell et al. is used for preventing aggregation and not intended for therapeutic use as being considered relevant to the present invention (see page 3, the last paragraph). The applicants' argument has been fully considered but it is found to be not persuasive.

Quibell et al. teach a peptide compound comprising (*a*) a peptide portion that is capable of forming β-structure on its *N-terminal* region (residues 1-22) (*equivalent to the first edge of the instant application*) with other peptide molecule, and (*b*) a peptide portion in which residues 20, 25, 29, 33 and 38 have been Nα-substituted with N-(2-hydroxy-4-methoxybenzyl), *i.e.*, Hmb, on its *C-terminal* region (residues 25-43), and (*c*) a dipeptide (residues 23-24) connecting the

peptide portion *a* and portion *b* (see the peptide structure depicted on page 2020). Quibell et al. further teach that the C-terminal portion peptide (*equivalent to the second edge β-strand forming section of the instant application*) comprises at least four consecutive α-L-amino acid residues (residues 39-42: VVIA"), all of which sterically permit the said portion to form a β-structure (e.g., β-hairpin, see Figure 1), and that the said portion has the following structural features: (i) at least one of the amino acid residues is Nα-substituted, e.g., Hmb-substituted (*note that claim1 recites "at least one of which is an Nα-substituted α-L-amino acid residue", indicating that, within the β-strand forming section, minimal number of the Nα-substituent is one residue*); (ii) the side chains of the peptide can form interchain β-structure, e.g., for non-covalent interactions with neighboring said chains of a target molecule β-structure, this is because the Quibell' peptide is a β-amyloid derivative which is a typical β-structure forming peptide, and in natural forms, the β-amyloid polypeptides tend to aggregate via β-structure interactions. The above Quibell et al. teachings meet the limitation set forth in the instant claim 1. Please note that the Quibell' reference incorporates reference 18, i.e., Burdick, D. et al. (1992) *J. Biol. Chem.* 267, 546-554 (see page 2020, the right column, the last paragraph), which teaches that the peptide is a β-amyloid wherein residues 1-43 are capable of forming β-structure. Thus, the structural features of the Quibell's peptide compound meet the claim 1 limitations.

Please note claim 1 is a composition claim. The above-mentioned applicants argument discuss therapeutic use of the claimed composition. This is unpersuasive because there is no patentable weight associated with the therapeutic use of the composition. Note that structure and

biological activity of the claimed composition will not be altered due to the use of the composition thereof.

Also, note that the Quibell's reference does not set forth or suggest removing all of Nα-substituents, i.e., the Hmb groups.

In view of the above statements, therefore, the claimed invention does not constitute a special technical feature linking all claims, as defined by PCT Rule 13.2 and 37 CFR 1.475(a), as a single contribution over the art, and a holding of lack of unity is therefore proper. Therefore, the requirement is still deemed proper and is therefore made FINAL.

The pending claims 1-28 and 43 are examined in this Office action. Claims 29-42 and 44-45 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected inventions.

IDS

The references of IDS filed 2 May 2002 and IDS filed 11 June 2002.

Please note that Applicants' submission of IDS filed 23 May 2002 is incomplete since it contains no copies of the non-patent literatures which are lined-through indicated in the corresponding PTO 1449 forms of said IDS. The references, which are not lined through, have been considered by Examiner. The instant application fails to comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609. The information referred to therein has not been considered as to the merits. Applicant is advised that the date of any re-submission of any items of information contained in this information disclosure statement or the submission of any missing items will be the date of submission for purposes of determining compliance with the requirements based on

the time of filing the statement, including all certification requirements for statements under 37 CFR 1.97(e). See MPEP § 609 ¶ C (1).

Specification Objection

The disclosure is objected to because of the following informalities:

In page 4, line 24, "SEQ ID NO:1" should be inserted after "KLVFF"; the same change should be made throughout the specification.

In page 4, line 34, "SEQ ID NO:3" should be inserted after "KKLVFFA"; the same change should be made throughout the specification.

In page 9, line 30, "COO" should be changed to "COOR"; line 31, change "COS" to "COSR", and after "COS" insert "(thioester)"; and, line 31, "CSS" should be pointed out for what kind of compound it stands, and after "CSS" "(thioester)" should be deleted because "CSS" does not stands for thioester.

In page 16, lines 35, "monomers are amino-acids and" is suggested to change to "amino acid residues" because the term "monomers" are NOT commonly accepted term for describing amino acids of polypeptide.

In page 22, line 19, "SEQ. ID. NO. 1" should be changed to "SEQ ID NO:1". The same change should be made throughout the specification.

In clam 1, "α-L-amino-acid" should be changed to ""α-L-amino acid" since "amino-acid" is not commonly accepted form. The same change is advised to be made for claims 2-45.

In claim 8, "β-sheet propensity" should be changed to "β-structure propensity" because β-structure encompasses β-sheet.

Claims 16 and 17 are objected to as non-compliant with 37 C.F.R. 1.821 (d). The "SEQ ID NO:_" is missing from the claims after the peptide sequence "KLVFFAE".

In claim 21, "inclusion" should be changed to "incorporation".

In claim 26, "SEQ. ID. NO. 1" should be changed to "SEQ ID NO:1".

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter that the applicant regards as his invention.

Claims 1-28 and 43 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites "peptide-containing molecule"; it is unclear as to whether or not peptide contains the molecule, or molecule comprises the peptide. Claim 1 is ambiguous in "and any two successive..." (see line 13 of the claim) wherein "and" renders the claim indefinite because the immediate preceding limitation has recited "and at least one of which ...". Claim 1 sets forth that, among residues of the second edge of the claimed peptide compound, at least one of these residues is an Nα-substituted residue. Here, "at least one" is NOT in accordance with the recitation "any two successive Nα-substituted α-L-amino acid residues". Thus, claim 1 recitation "and any two successive..." is indefinite. In addition, claim 1 is indefinite in the recitation "*the β-strand forming section of peptide comprises a sequence of at least four consecutive α-L-amino acid residues*" and the recitation "*any two successive residues are separated by odd number of consecutive Nα-substituted α-L-amino acid residues*"; theses two recitations are paradox or

contradictory from each other since the "odd number of consecutive" denotes at least **three** residues which is in combination with "any **two** successive residues"; and thus, the β-strand forming section comprises at least five (3 + 2 =5) residues. This is not consistent with the recitation "at least **four**...". Further, claim 1 is unclear in "at least one of which ..." because herein the phrase "of which" can ambiguously refer to at least four residues only, or the residues of entire β-strand forming section that comprises a sequence of at least four consecutive amino acid residues. For examination purpose, it is assumed that the limitation of "at least one amino acid residue within the β-strand forming section is Nα-substituted" describes the structural feature of the claimed peptide compound. The dependent claims are also rejected.

Claim 4 recites "with another β-strand"; the recitation is unclear as to whether or not it refers to intermolecular or intermolecular β-strand. Also, claim 4 lacks antecedent basis for the recitation "the Nα-substituent".

Claim 6 recites "a group that is connected to the Nα atom by an oxygen atom within it"; the term "it" in the recitation is not apparent as to what it refers; does it refer to said "group" or the subgroup. See also the recitation "a CH_2 subgroup within it".

Claim 12 is indefinite in "the side chain... extends beyond..." because "extends beyond" is unclear as to whether or not it refers to non-covalent interaction between the side chains, or steric imposition but not chemical interaction; here, the side chain interaction is intra-molecular side-chain interaction.

Claim 15 is indefinite because glycine residue has no side chain; and thus, glycine is not a member of the recited Markush group in the claim.

Claim 18 recitation "mimic thereof" is indefinite because it is not clear regarding whether or not the "mimic" refers to non-peptide compound or peptide mimetic.

Claim 19 recites "the peptide is preceded by, followed by..."; the recitation is unclear as to whether or not said peptide is a fusion peptide in which, besides the claimed membrane-penetrating section of the peptide, there is additional peptide component(s), and whether or not the β-strand forming section is immediately or indirectly (interrupted by additional component) preceded or followed the membrane-penetrating section of the peptide. Additionally, the phrase "such as" renders claim 19 indefinite because it is unclear whether the limitations following the phrase (e.g., "cell membranes and the blood-brain barrier") are part of the claimed invention. See MPEP § 2173.05(d).

Claim 20 is indefinite because the claim appears to contain an open ended Markush group. See "or arginine" wherein "or" renders the claim indefinite. Markush language requires close language.

Claim 22 recitation "forms part of a larger peptide" is unclear as to how large said peptide is; and whether or not the said peptide is a multimer or a fusion peptide.

Claim 23 recites "functional component"; the specification does not define this recitation; does it encompasses (i) any active chemical group or moiety or compound; or (ii) functional amino acid(s); or (iii) any biopolymer (e.g., fatty acid, polysaccharide or polynucleotide)?

Claim 25 recites "an amide or ester linkage formed with C-terminal carboxyl group or ... or N-terminal amino group"; the recitation is unclear because amide linkage does not formed with the *carboxyl* group, and ester linkage does not formed with the *amine* group. Rewriting the

claim in a proper format will obviate the rejection. Also, claims 25 is not apparent in "the full peptide" because it can refer to a peptide entity consisting of multimer, e.g., dimer, or, a full-length peptide.

Claim 27 recitation "backbone peptide groups" is ambiguous because it is not apparent regarding whether or not the said *groups* include *hydrogens* of backbone nitrogens or/and backbone carboxyl groups. See also claim 28.

Claim 28 is indefinite in the recitation "N- or C-substituted form" because it is unclear as to whether or not the recitation refers to the substituted form at Nα, or backbone carboxyl moiety, or refers to N-terminus or substituted form.

Claim Rejections - 35 USC §102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 4-13, 15, 22-24 and 26 are rejected under 35 U.S.C. 102(b) as being anticipated by Quibell M. et al. (*J. Chem. Soc. Perkin. Trans* (1995) 1, 2019-2024) as is evidenced by the known fact disclosed in the reference by Miller S. M. et al. (Drug Dev. Res. (1995) 35, 20-32).

Quibell et al. teach a peptide compound comprising (*a*) a peptide portion that is capable of forming β-structure on its *N-terminal* region (residues 1-22) (*equivalent to the first edge of the*

instant application) with other peptide molecule, and (*b*) a peptide portion in which residues 20, 25, 29, 33 and 38 have been Nα-substituted with N-(2-hydroxy-4-methoxybenzyl), *i.e.*, Hmb, on its *C-terminal* region (residues 25-43), and (*c*) a dipeptide (residues 23-24) connecting the peptide portion *a* and portion *b* (see the peptide structure depicted on page 2020). Quibell et al. further teach that the C-terminal portion peptide (*equivalent to the second edge β-strand forming section of the instant application*) comprises at least four consecutive α-L-amino acid residues (residues 39-42: VVIA"), all of which sterically permit the said portion to form a β-structure (e.g., β-hairpin, see Figure 1), and that the said portion has the following structural features: (i) at least one of the amino acid residues is Nα-substituted, e.g., Hmb-substituted (*note that claim1 recites "at least one of which is an Nα-substituted α-L-amino acid residue", indicating that, within the β-strand forming section, minimal number of the Nα-substituent is one residue*); (ii) the side chains of the peptide can form interchain β-structure, e.g., for non-covalent interactions with neighboring said chains of a target molecule β-structure, this is because the Quibell' peptide is a β-amyloid derivative which is a typical β-structure forming peptide, and in natural forms, the β-amyloid polypeptides tend to aggregate via β-structure interactions. The above Quibell et al. teachings meets the limitation set forth in the instant claim 1. Please note that the Quibell' reference incorporates reference 18, i.e., Burdick, D. et al. (1992) *J. Biol. Chem.* 267, 546-554 (see page 2020, the right column, the last paragraph), which teaches that the peptide is a β-amyloid wherein residues 1-43 are capable of forming β-structure.

The Quibell et al. peptide compound is synthesized for preventing hydrogen boding between β-structures of individual polypeptides (i.e., interchain or intermolecular interaction)

thereby inhibiting intermolecular aggregation of the said polypeptides (see page 2019) while said peptide can form a intermolecular β-structure (see Figure 1). The Quibell et al. teaching anticipates the instant claim 4.

Since the current invention is directed to composition, and since proteolysis-resistance is an *intrinsic property* of the Nα-substituted polypeptide as is evidenced by Miller et al. reference, the above Quibell et al. teachings are applied to the instant claim 5.

Since claim 6 recites the limitation that the Nα-substituted group is "a group that is connected to the Nα atom by a CH_2 methylene group", and since the Quibell's peptide compound contains N-(2-hydroxy-4-methoxybenzyl) group which is linked to Nα through methylene group, the above Quibell's teachings anticipate the instant claim 6.

In Figure 1, Quibell et al. show that the C-terminal segment (*equivalent to the β-strand-forming section of the claimed peptide*) forms a β-hairpin structure, wherein aliphatic said chain groups of hydrophobic amino acid residues (e.g., Val, Ile Ala) participate in hydrophobic stacking of β-structures, which anticipates the instant claim 7.

Also, Figure 1 shows that residue 36 (valine) and residue 41 (valine) participate in β-structure formation, and have been labeled of high propensity (> 1.00) of forming β-structure. The Quibell et al. teaching meets the limitation set forth in the instant claim 8.

Quibell et al. teach that the β-forming peptide comprises amino acids which have side chain that promote β-structure formation, e.g., 3-methylvaleric group (Leu), isovaleric group (Val), methyl group (Ala) and 3-methylvaleric group (Ile) (see the peptide structure depicted in page 2020); these groups have hydrophobic characters. The Quibell's teaching anticipates the instant claims 9-10.

Quibell et al. teach that the β-forming peptide contains glycine residues (see the peptide structure depicted in page 2020) which hinders the stacking (i.e., hydrophobic interaction) because glycine has no said chain, which anticipates the instant claim 11.

Figure 1 (*a*) shows the said chain interaction in the β-forming peptide, which anticipates the instant claim 12.

In "Result and Discussion" section, Quibell et al. teach the β-forming peptide comprising Hmb substituents is detected and analyzed by HPLC-assisted electrospray mass spectrometry (see page 2020, the left column), wherein Hma group gives rise to characteristic peaks in the mass spectrometric profile (see Figure 2). The Quibell et al. teaching anticipates the instant claim 13.

Quibell et al. teach that Nα hydrogens of glycine residues 20, 25, 29, 33 and 38 of β-forming peptide are substituted with Hmb groups (see the peptide structure depicted in page 2020), which meets the limitation set forth in the instant claim 15.

Since the N-terminus of the Quibell's peptide compound is unmodified, i.e., comprises free amine group, the above teachings anticipate the instant claim 22.

In Figure 1 (*a*), Quibell et al. teach that the said peptide is attached to a resin, which anticipates the instant claims 23-24.

Also, Quibell et al. teach that the said peptides form interchain β-structures (see Figure 1). Of the peptides, there are (i) the target β-strands and (ii) the β-strand forming section of the peptides, and both of which are β-amyloid polypeptide derivatives comprising KLVFF sequence (see residues 16-20 of the peptide depicted at page 2020). Note that the β-amyloid polypeptides are of prone of forming interchain β-strand formation. Therefore, there exists interaction between

the target β-strands and the β-strand forming section of the peptides (se page 2019). Thus, the above Quibell' teaching anticipates the instant claim 26.

Provisional Rejection, 35 U.S.C. 101, Double Patenting

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title.

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process... may obtain a patent therefor..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

Claims 1-4, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 19, 20, 22, 23, 24, 25, 26, 27, 28 and 43 are rejected under 35 U.S.C. 101 as claiming the same invention as claims 1-4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 24, 25, 26 and 41of U.S. Application No. 10030138, respectively. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Samuel Wei Liu whose telephone number is 571-272-0949. The examiner can normally be reached from 9:00 a.m. to 5:00 p.m. on weekdays. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Christopher Low, can be reached on 571-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 703 308-4242 or 703 872-9306 (official) or 703 872-9307 (after final). Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703 305-4700.

Samuel Wei Liu, Ph.D.
Art Unit 1653, Examiner
June 4, 2004

KAREN COCHRANE CARLSON, PH.D
PRIMARY EXAMINER